

# Pathophysiologic Approach to Therapy in Patients With Newly Diagnosed Type 2 Diabetes

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Two general approaches to the treatment of type 2 diabetes mellitus (T2DM) have been advocated. 1) A “guideline” approach that advocates sequential addition of antidiabetes agents with “more established use” (1); this approach more appropriately should be called the “treat to failure” approach, and deficiencies with this approach have been discussed (2). And 2) a “pathophysiologic” approach using initial combination therapy with agents known to correct established pathophysiologic defects in T2DM (3). Within the pathophysiologic approach, choice of antidiabetes agents should take into account the patient’s general health status and associated medical disorders. This individualized approach, which we refer to as the ABCD(E) of diabetes treatment (4), has been incorporated into the updated American Diabetes Association (ADA) guidelines (5).

A = Age

B = Body weight

C = Complications (microvascular and macrovascular)

D = Duration of diabetes

E = Life Expectancy

E = Expense

Even though physicians must be cognizant of these associated conditions (ABCDE) when initiating therapy in newly diagnosed T2DM patients, we believe that the most important consideration is to

select antidiabetes agents that correct specific pathophysiologic disturbances present in T2DM and that have complementary mechanisms of action. Although it has been argued that the pathogenesis of T2DM differs in different ethnic groups (6), evidence to support this is weak. Although the relative contributions of  $\beta$ -cell failure and insulin resistance to development of glucose intolerance may differ in different ethnic groups (6), the core defects of insulin resistance in muscle/liver/adipocytes and progressive  $\beta$ -cell failure (3) are present in virtually all T2DM patients and must be treated aggressively to prevent the relentless rise in HbA<sub>1c</sub> that is characteristic of T2DM.

In subsequent sections, we provide a review of the natural history of T2DM, specific pathophysiologic abnormalities responsible for T2DM, currently available antidiabetes agents and their mechanism of action, recommended glycemic goals, and use of combination therapy based upon reversal of pathophysiologic defects present in T2DM. We will not address expense but recognize that this is an important consideration in choosing any antidiabetes regimen.

## Overview of T2DM: pathophysiology and general therapeutic approach

T2DM is a complex metabolic/cardiovascular disorder with multiple pathophysiologic abnormalities. Insulin resistance

in muscle/liver and  $\beta$ -cell failure represent the core defects (7,8).  $\beta$ -Cell failure occurs much earlier in the natural history of T2DM and is more severe than previously thought (9–12). Subjects in the upper tertile of impaired glucose tolerance (IGT) are maximally/near-maximally insulin resistant and have lost >80% of their  $\beta$ -cell function. In addition to muscle, liver, and  $\beta$ -cells (“triumvirate”) (7), adipocytes (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance),  $\alpha$ -cells (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance and neurotransmitter dysregulation) play important roles in development of glucose intolerance in T2DM individuals (3). Collectively, these eight players comprise the “ominous octet” (Fig. 1) and dictate that 1) multiple drugs used in combination will be required to correct the multiple pathophysiological defects, 2) treatment should be based upon reversal of known pathogenic abnormalities and not simply on reducing HbA<sub>1c</sub>, and 3) therapy must be started early to prevent/slow progressive  $\beta$ -cell failure that is well established in IGT subjects. A treatment paradigm shift is recommended in which combination therapy is initiated with agents that correct known pathogenic defects in T2DM and produce durable reduction in HbA<sub>1c</sub> rather than just focusing on the glucose-lowering ability of the drug.

## Natural history of T2DM

Individuals destined to develop T2DM inherit genes that make their tissues resistant to insulin (2,8,13–15). In liver, insulin resistance is manifested by glucose overproduction during the basal state despite fasting hyperinsulinemia (16) and impaired suppression of hepatic glucose production (HGP) by insulin (17), as occurs following a meal (18). In muscle (17,19,20), insulin resistance is manifest by impaired glucose uptake after carbohydrate ingestion, resulting in postprandial hyperglycemia (18). Although the origins of insulin resistance can be traced to their genetic background (8,14,15), the current diabetes epidemic is related to the

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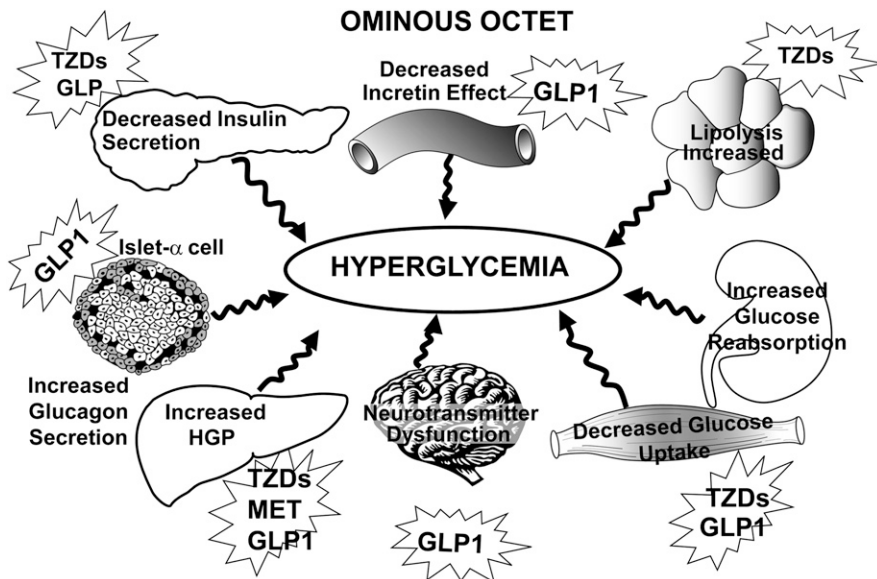
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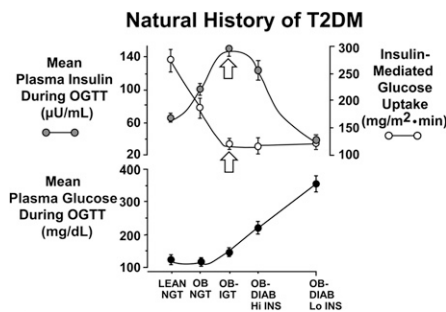
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See accompanying article, p. S139.



**Figure 1**—The ominous octet (3) depicting the mechanism and site of action of antidiabetic medications based on the pathophysiologic disturbances present in T2DM.

epidemic of obesity and physical inactivity (21), which are insulin-resistant states (22) and place stress on pancreatic  $\beta$ -cells to augment insulin secretion to offset insulin resistance (2,3,8). As long as  $\beta$ -cells augment insulin secretion sufficiently to offset the insulin resistance, glucose tolerance remains normal (2,3,8,23–29). However, with time  $\beta$ -cells begin to fail, and initially postprandial plasma glucose levels and subsequently fasting plasma glucose begin to rise, leading to overt diabetes (2,3,8). Thus, it is progressive  $\beta$ -cell failure that determines the rate of disease progression. The natural history of T2DM described above (2,3) is depicted by a prospective study carried out by DeFronzo



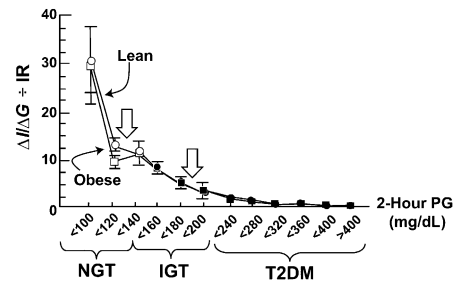
**Figure 2**—Natural history of T2DM. The plasma insulin response depicts the classic Starling’s Curve of the Pancreas. See text for a detailed explanation (7). Upper panel: Insulin-mediated glucose disposal (insulin clamp technique) and mean plasma insulin concentration during OGTT. Lower panel: Mean plasma glucose concentration during OGTT. DIAB, T2DM; Hi, high; Lo, low; OB, obese.

(3); Jallut, Goyal, and Munger (30); and Felber et al. (31) (Fig. 2).

**$\beta$ -Cell function**

Although the plasma insulin response to insulin resistance is increased early in the natural history of T2DM (Fig. 2), this does not mean that  $\beta$ -cells are functioning normally (3). Simply measuring the plasma insulin response to a glucose challenge does not provide a valid index of  $\beta$ -cell function (32).  $\beta$ -Cells respond to an increment in glucose ( $\Delta G$ ) with an increment in insulin ( $\Delta I$ ). Thus, a better measure of  $\beta$ -cell function is  $\Delta I/\Delta G$ . However,  $\beta$ -cells also increase insulin secretion to offset insulin resistance and maintain normoglycemia (9,10,12,23,32,33). Thus, the gold standard measure of  $\beta$ -cell function in vivo in man is the insulin secretion/insulin resistance (disposition) index ( $\Delta I/\Delta G \div IR$ ).

Figure 3 depicts the insulin secretion/insulin resistance index in normal glucose tolerant (NGT), IGT, and T2DM subjects as a function of 2-h plasma glucose during oral glucose tolerance test (OGTT) (2,9,10,12). Subjects in the upper tertile of NGT (2-h plasma glucose 120–139 mg/dL) have lost >50% of  $\beta$ -cell function, while subjects in upper tertile of IGT (2-h plasma glucose 180–199 mg/dL) have lost ~80% of  $\beta$ -cell function (Fig. 3). Similar conclusions are evident from other publications (24,27,34,35). The therapeutic implications of these findings are obvious. When the diagnosis of diabetes is made, the patient has lost ~80% of their  $\beta$ -cell



**Figure 3**—Insulin secretion/insulin resistance (disposition) index ( $\Delta I/\Delta G \div IR$ ) during OGTT in individuals with NGT, IGT, and T2DM as a function of the 2-h plasma glucose (PG) concentration in lean and obese subjects (9–12).

function, and it is essential that physicians intervene with therapies known to correct established pathophysiological disturbances in  $\beta$ -cell function. Even more ominous are observations of Butler et al. (36), who demonstrated that as individuals progress from NGT to IFG, there is significant loss of  $\beta$ -cell mass that continues with progression to diabetes. Similar results have been published by others (37,38) and indicate that significant loss of  $\beta$ -cells occurs long before onset of T2DM, according to current diagnostic criteria (1).

In summary, although insulin resistance in liver/muscle is well established early in the natural history of T2DM, overt diabetes does not occur in the absence of progressive  $\beta$ -cell failure.

**Insulin resistance**

The liver and muscle are severely resistant to insulin in T2DM (rev. in 2,3,8).

**Liver.** After an overnight fast, the liver produces glucose at ~2 mg/kg/min (2,16). In T2DM, the rate of basal HGP is increased, averaging ~2.5 mg/kg/min (2,16). This amounts to addition of an extra 25–30 g glucose to the systemic circulation nightly and is responsible for the increased fasting plasma glucose concentration. This hepatic overproduction of glucose occurs despite fasting insulin levels that are increased two- to three-fold, indicating severe hepatic insulin resistance.

**Muscle.** With use of the euglycemic insulin clamp with limb catheterization (2,3,17,19,20,39,40), it has conclusively been demonstrated that lean, as well as obese, T2DM individuals are severely resistant to insulin and that the primary site of insulin resistance resides in muscle. Multiple intramyocellular defects in insulin action have been documented in

T2DM (rev. in 2,3,8,40), including impaired glucose transport/phosphorylation (17), reduced glycogen synthesis (39), and decreased glucose oxidation (17). However, more proximal insulin signaling defects play a paramount role in muscle insulin resistance (3,40–42).

### Ominous octet

In addition to the triumvirate ( $\beta$ -cell failure and insulin resistance in muscle and liver), at least five other pathophysiologic abnormalities contribute to glucose intolerance in T2DM (3) (Fig. 1): 1) adipocyte resistance to insulin's antilipolytic effect, leading to increased plasma FFA concentration and elevated intracellular levels of toxic lipid metabolites in liver/muscle and  $\beta$ -cells that cause insulin resistance and  $\beta$ -cell failure/apoptosis (17); 2) decreased incretin (glucagon-like peptide [GLP]-1/glucose-dependent insulinotropic polypeptide [GIP]) effect resulting from impaired GLP-1 secretion (43) but, more importantly, severe  $\beta$ -cell resistance to the stimulatory effect of GLP-1 and GIP (44,45); 3) increased glucagon secretion by  $\alpha$ -cells and enhanced hepatic sensitivity to glucagon, leading to increased basal HGP and impaired HGP suppression by insulin (46,47); 4) enhanced renal glucose reabsorption contributing to maintenance of elevated plasma glucose levels (48,49); and 5) central nervous system resistance to the anorectic effect of insulin and altered neurosynaptic hormone secretion contributing to appetite dysregulation, weight gain, and insulin resistance in muscle/liver (50–52).

### Implications for therapy

The preceding review of pathophysiology has important therapeutic implications: 1) effective treatment will require multiple drugs in combination to correct the multiple pathophysiological defects, 2) treatment should be based upon established pathogenic abnormalities and not simply on HbA<sub>1c</sub> reduction, and 3) therapy must be started early in the natural history of T2DM to prevent progressive  $\beta$ -cell failure.

Figure 1 displays therapeutic options as they relate to key pathophysiological derangements in T2DM (Fig. 1). In liver, both metformin (53–55) and thiazolidinediones (TZDs) (56–62) are potent insulin sensitizers and inhibit the increased rate of HGP. In muscle, TZDs are potent insulin sensitizers (56–58,61,63), whereas metformin is, at best, a weak insulin sensitizer (53,55,64). Since TZDs work

through the insulin signaling pathway (65), whereas metformin works through the AMP kinase pathway (66), combination TZD/metformin therapy gives a completely additive effect to reduce HbA<sub>1c</sub> (67–72). Further, hypoglycemia is not encountered because these drugs are insulin sensitizers and do not augment insulin secretion. In adipocytes, TZDs are excellent insulin sensitizers and potent inhibitors of lipolysis (73). TZDs also mobilize fat out of muscle, liver, and  $\beta$ -cells, thereby ameliorating lipotoxicity (57,62,63,74–76).

Although weight loss has the potential to improve both the defects in insulin sensitivity and insulin secretion (77), two meta-analyses involving 46 published studies demonstrated that the ability to maintain the initial weight loss is difficult (78,79). In the following sections, we will focus on pharmacologic agents—as monotherapy and combination therapy—that have been proven to reverse pathophysiologic abnormalities in T2DM.

In the  $\beta$ -cell, sulfonylureas and glinides augment insulin secretion (80), but only TZDs (81–83) and GLP-1 analogs (84–86) improve and preserve  $\beta$ -cell function and demonstrate durability of glycemic control (70,82–85,87–93). Importantly, TZDs and GLP-1 analogs cause durable HbA<sub>1c</sub> reduction for up to 5 and 3.5 years, respectively (82,93). Although dipeptidyl peptidase inhibitors (DPP4i) augment insulin secretion (94), their  $\beta$ -cell effect is weak compared with GLP-1 analogs and they begin to lose efficacy (manifested by rising HbA<sub>1c</sub>) within 2 years after initiation of therapy (95,96). Despite the potent effects of TZDs and GLP-1 agonists on  $\beta$ -cells, the two most commonly prescribed drugs in the U.S. and worldwide are sulfonylureas and metformin, neither of which exerts any  $\beta$ -cell protective effect. This is a major concern, since progressive  $\beta$ -cell failure is the primary pathogenic abnormality responsible for development of T2DM and progressive HbA<sub>1c</sub> rise (Fig. 3).

GLP-1 analogs augment and preserve  $\beta$ -cell function for at least 3 years (84). This protective effect has its onset within 24 h (86) and persists as long as GLP-1 therapy is continued (84,85,93). Further, both exenatide and liraglutide promote weight loss, inhibit glucagon secretion, and delay gastric emptying, reducing postprandial hyperglycemia (45,93,97–99). Weight loss depletes lipid from muscle and liver, improving muscle and hepatic insulin sensitivity (84,85). GLP-1

analog also correct multiple cardiovascular risk factors (rev. in 100) and, thus, have the potential to reduce cardiovascular events (101,102). Although DPP4i share some characteristics with GLP-1 analogs, they do not raise plasma GLP-1 levels sufficiently to offset  $\beta$ -cell resistance to GLP-1 (103). Not surprisingly, their ability to augment insulin secretion and reduce HbA<sub>1c</sub> is considerably less than GLP-1 analogs (94,104,105), and they do not promote weight loss (94). In a 1-year study involving 665 metformin-treated T2DM patients, HbA<sub>1c</sub> reduction with sitagliptin (0.9%) was significantly less than liraglutide dosed at 1.2 mg/day ( $\Delta$ HbA<sub>1c</sub> = 1.2%) or 1.8 mg/day ( $\Delta$ HbA<sub>1c</sub> = 1.8%) (105). In a short-term, mechanism-of-action, crossover study, exenatide was far superior to sitagliptin in reducing glucose area under the curve and 2-h glucose after a meal, increasing insulin secretion, inhibiting glucagon secretion, and promoting weight loss (104). Metformin increases GLP-1 secretion by intestinal L-cells (106–108), and the combination of metformin plus DPP4i may exert a more durable effect on  $\beta$ -cell function. The major mechanism of action of DPP4i to improve glycemic control is mediated via inhibition of glucagon secretion with subsequent decline in HGP (109).

Although not yet approved by U.S. regulatory agencies, sodium glucose transporter 2 inhibitors (approved in Europe) demonstrate modest efficacy in reducing HbA<sub>1c</sub>, promote weight loss, reduce blood pressure, and can be added to any antidiabetic agent (48,110).

### Instituting therapy in newly diagnosed T2DM patients

When initiating therapy in newly diagnosed T2DM patients, the following considerations are of paramount importance:

1. Therapy should have the ability to achieve the desired level of glycemic control, based upon starting HbA<sub>1c</sub>. According to the ADA, European Association for the Study of Diabetes (EASD), and American Association of Clinical Endocrinologists (AACE), the desired HbA<sub>1c</sub> is 6.5% (EASD and AACE) or 7.0% (ADA) (5,111). However, we believe that in newly diagnosed diabetic patients without cardiovascular disease, the optimal HbA<sub>1c</sub> should be  $\leq$ 6.0%, while avoiding adverse events, primarily hypoglycemia. This is consistent with the expanded ADA/EASD statement (5).

- In most newly diagnosed diabetic patients, monotherapy will not reduce HbA<sub>1c</sub> <6.5–7.0% or, most optimally, <6.0%, and combination therapy will be required.
- Importantly, medications used in combination therapy should have an additive effect, and individual drugs should correct established pathophysiologic disturbances in T2DM. If antidiabetes medications do not correct underlying pathogenic abnormalities, long-term durable glycemic control cannot be achieved.
- Progressive  $\beta$ -cell failure is responsible for progressive HbA<sub>1c</sub> rise in T2DM (3). Therefore, medications used to treat T2DM should preserve or improve  $\beta$ -cell function to ensure durable glycemic control.
- Because insulin resistance is a core defect in T2DM and exacerbates the decline in  $\beta$ -cell function, medications also should ameliorate insulin resistance in muscle/liver.
- T2DM is associated with an increased incidence of atherosclerotic cardiovascular complications. Therefore, it is desirable that drugs exert beneficial effects on cardiovascular risk factors and decrease cardiovascular events.
- Since obesity is a major problem in diabetic individuals, combination therapy should be weight neutral and, if possible, promote weight loss.
- Combination therapy should be safe and not exacerbate underlying medical conditions.

No single antidiabetes agent can correct all of the pathophysiologic disturbances present in T2DM, and multiple agents, used in combination, will be required for optimal glycemic control. Further, the HbA<sub>1c</sub> decrease produced by a single antidiabetes agent, e.g., metformin, sulfonylurea, TZD, GLP-1 analog, is in the range of 1.0–1.5% depending upon the starting HbA<sub>1c</sub> (5). Thus, in newly diagnosed T2DM with HbA<sub>1c</sub> >8.0–8.5%, a single agent is unlikely to achieve HbA<sub>1c</sub> goal <6.5–7.0%, and virtually no one will achieve HbA<sub>1c</sub> <6.0%. When maximal-dose metformin, sulfonylurea, or TZD is initiated as monotherapy, <40% of newly diagnosed T2DM subjects can be expected to achieve HbA<sub>1c</sub> <6.5–7.0%. Thus, most patients with HbA<sub>1c</sub> >8.0–8.5% will require initial combination therapy to reach HbA<sub>1c</sub> <6.5–7.0%. Moreover, because different agents lower plasma glucose via different mechanisms, combination

therapy will have an additive effect to reduce HbA<sub>1c</sub> compared with each agent alone. Simultaneous correction of the  $\beta$ -cell defect and insulin resistance is more likely to cause durable HbA<sub>1c</sub> reduction. Lastly, combination therapy allows use of submaximal doses of each antidiabetes agent, resulting in fewer side effects (112).

In summary, initiating therapy with multiple antidiabetes agents in newly diagnosed T2DM patients, especially those with HbA<sub>1c</sub> >8.0–8.5%, represents a rational approach to achieve the target HbA<sub>1c</sub> level while minimizing side effects. Indeed, AACE recommends starting newly diagnosed diabetic subjects with HbA<sub>1c</sub> >7.5% on multiple antidiabetes agents (111).

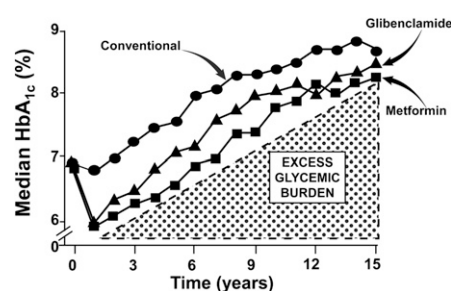
### “Treat to fail” algorithm

The 2009 ADA/EASD algorithm (1) recommended initiation of therapy with metformin to achieve HbA<sub>1c</sub> <7.0%, followed by, importantly, sequential addition of a sulfonylurea. If sulfonylurea addition failed to reduce HbA<sub>1c</sub> <7.0%, addition of basal insulin was recommended. Although the revised 2012 ADA/EASD algorithm (5) includes newer antidiabetes agents (GLP-1 receptor agonists, DPP4i, and TZDs) as potential choices if metformin fails, the initial box in the treatment algorithm still depicts sequential addition of sulfonylurea and then insulin to maintain HbA<sub>1c</sub> <7.0%. This algorithm has little basis in pathophysiology and more appropriately should be called the treat to fail algorithm. Moreover, it does not consider the starting HbA<sub>1c</sub> or need for initial combination therapy in most newly diagnosed T2DM patients, especially if HbA<sub>1c</sub> goal <6.0–6.5% is desired, as suggested by us (4) and by the 2012 ADA/EASD consensus statement (5). Because  $\beta$ -cell failure is progressive (9–12,24–30,34,35,113,114) and results in loss of  $\beta$ -cell mass (36–38), it is essential to intervene with agents that normalize HbA<sub>1c</sub> and halt the progressive  $\beta$ -cell demise (Fig. 3). Failure to do so will result in the majority of T2DM patients progressing to insulin therapy, as demonstrated in the UK Prospective Diabetes Study (UKPDS) (113,114).

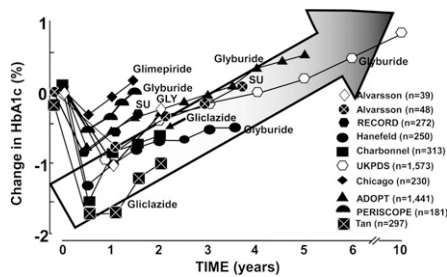
**Sulfonylureas/glinides: the treat to fail approach.** Until recently (5), sulfonylureas have been considered the drug of choice for add-on therapy to metformin (1). In large part, this is attributed to their low cost and rapid onset of hypoglycemic

effect. However, they lack “glycemic durability” and within 1–2 years lose their efficacy, resulting in steady HbA<sub>1c</sub> rise to or above pretreatment levels (107,108) (Figs. 4 and 5). Although long-term studies examining glycemic durability with glinides (nateglinide, repaglinide) in T2DM are not available, nateglinide failed to prevent prediabetic (IGT) patients from progressing to T2DM (115). In a 2-year study in newly diagnosed T2DM subjects, durability of nateglinide plus metformin was comparable with glyburide plus metformin (116) and both groups experienced a small but progressive HbA<sub>1c</sub> rise after the first year. Since deterioration in glycemic control is largely accounted for by progressive  $\beta$ -cell failure (3), it is clear that both sulfonylureas and glinides fail to prevent the progressive decline in  $\beta$ -cell function characteristic of T2DM. Consistent with this, in vitro studies have demonstrated a proapoptotic  $\beta$ -cell effect of sulfonylureas and glinides (117–120).

UKPDS conclusively demonstrated that sulfonylureas exerted no  $\beta$ -cell protective effect in newly diagnosed T2DM patients (starting HbA<sub>1c</sub> = 7.0%) over a 15-year follow-up (113,114). After an initial HbA<sub>1c</sub> drop, sulfonylurea-treated patients experienced progressive deterioration in glycemic control that paralleled HbA<sub>1c</sub> rise in conventionally treated individuals (Fig. 4). Moreover, some studies have suggested that sulfonylureas may accelerate atherogenesis (121,122). Similarly, metformin-treated patients in UKPDS, after initial HbA<sub>1c</sub> decline (secondary to inhibition of HGP), also experienced progressive deterioration in glycemic control (123) (Fig. 4). With use of homeostasis model assessment of  $\beta$ -cell function, it was shown that the relentless



**Figure 4**—The effect of sulfonylurea (glibenclamide = glyburide) and metformin therapy on the plasma HbA<sub>1c</sub> concentration in newly diagnosed T2DM subjects in UKPDS. Conventionally treated diabetic subjects received diet plus exercise therapy (113,114).



**Figure 5**—Durability of glycemic control with sulfonylureas. Summary of studies examining the effect of sulfonylurea treatment versus placebo or versus active comparator on HbA<sub>1c</sub> in T2DM. See text for a more detailed discussion (70,82,87–92,113,114,124–127,131,132).

HbA<sub>1c</sub> rise observed with sulfonylureas and metformin resulted from progressive decline in  $\beta$ -cell function and that within 3–5 years, ~50% of diabetic patients required an additional pharmacologic agent to maintain HbA<sub>1c</sub> <7.0% (114,124–127). Although there is in vitro evidence that metformin may improve  $\beta$ -cell function (128,129), in vivo data from UKPDS and other studies (130) fail to support any role for metformin in preservation of  $\beta$ -cell function in humans. Metformin did reduce macrovascular events in UKPDS (123), although by today's standards the number of metformin-treated subjects ( $n = 342$ ) would be considered inadequate to justify any conclusions about cardiovascular protection. Other than its effect to reduce the elevated rate of basal and postprandial HGP (53,55,64), metformin does not correct any other component of the ominous octet (Fig. 1), and even its muscle insulin-sensitizing effect is difficult to demonstrate in absence of weight loss (53,55,64).

UKPDS was designed as a monotherapy study. However, after 3 years it became evident that monotherapy with neither metformin nor sulfonylureas could prevent progressive  $\beta$ -cell failure and stabilize HbA<sub>1c</sub> at its starting level (113,114,123–127). Therefore, study protocol was altered to allow metformin addition to sulfonylurea and sulfonylurea addition to metformin. Although addition of a second antidiabetes agent initially improved glycemic control, progressive  $\beta$ -cell failure continued and HbA<sub>1c</sub> rose progressively.

Numerous long-term (>1.5 years) active-comparator or placebo-controlled studies have demonstrated inability of sulfonylureas to produce durable HbA<sub>1c</sub> reduction in T2DM patients. These studies (70,83,87–92,113,131–133) showed that

after initial HbA<sub>1c</sub> decline, sulfonylureas (glyburide, glimepiride, and gliclazide) were associated with progressive decline in  $\beta$ -cell function with accompanying loss of glycemic control (Fig. 5). There are no exceptions to this consistent loss of glycemic control with sulfonylureas after the initial 18 months of therapy. Thus, evidence-based medicine demonstrates that the glucose-lowering effect of sulfonylureas is not durable and that loss of glycemic control is associated with progressive  $\beta$ -cell failure.

Sulfonylurea treatment does not correct any pathophysiologic component of the ominous octet (3) (Fig. 1) and is associated with significant weight gain and hypoglycemia (89,90). Although no study has clearly implicated sulfonylureas with an increased incidence of cardiovascular events, a deleterious effect of glibenclamide (glyburide) on the cardioprotective process of ischemic preconditioning has been demonstrated (134), while some (121,122,135–142) but not all (143,144) studies have suggested a possible association between sulfonylureas and adverse cardiovascular outcomes. Since metformin was the comparator in many of these studies (121,122,137,138,140–142), it is difficult to determine whether sulfonylureas increased or metformin decreased cardiovascular morbidity/mortality. In the study by Sillars et al. (143) the increased cardiovascular mortality/morbidity disappeared after adjusting for confounding variables, and failure to do so in other sulfonylurea studies may have clouded their interpretation. Among the sulfonylurea studies, the older sulfonylureas (i.e., glibenclamide) more commonly have been associated with increased adverse cardiovascular outcomes than the newer sulfonylurea agents (i.e., gliclazide and glimepiride) (139,144–146).

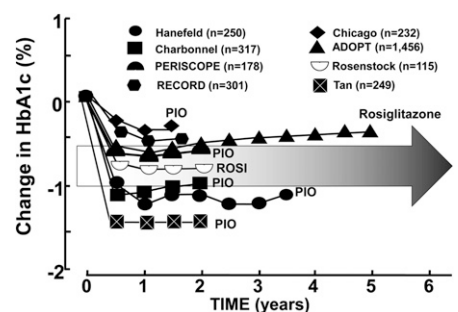
In summary, we believe that currently available insulin secretagogues (sulfonylureas and glinides) represent a poor option as add-on therapy to metformin. However, in many countries newer antidiabetes agents are not available or are expensive (ABCDE) (4). In such circumstances, sulfonylureas may be the only option.

**Antidiabetes agents known to reverse pathophysiologic defects**  
**Pioglitazone: unique benefits, unique side effects.** Rosiglitazone has been removed from the market or its use severely restricted because of cardiovascular safety concerns (147). Therefore, pioglitazone is

the only representative TZD. Pioglitazone is unique in that it both exerts  $\beta$ -cell protective effects (81) and is a powerful insulin sensitizer in muscle and liver (56–61,65,74–76). Thus, it is the only antidiabetes agent that corrects the core defects of insulin resistance and  $\beta$ -cell failure in T2DM. Not surprisingly, it has a durable effect to reduce HbA<sub>1c</sub> with low risk of hypoglycemia.

Eight long-term (>1.5 years) studies with TZDs (70,82,81–92) (Fig. 6) have demonstrated that, after initial decline in HbA<sub>1c</sub>, durability of glycemic control is maintained because of preservation of  $\beta$ -cell function in T2DM patients. Further, five studies demonstrate that TZDs prevent progression of IGT to T2DM (148–152). All five studies showed that, in addition to their insulin-sensitizing effect, TZDs had a major action to preserve  $\beta$ -cell function. In Actos Now for Prevention of Diabetes (ACT NOW), improved insulin secretion/insulin resistance (disposition) index was shown both with OGTT and frequently sampled intravenous glucose tolerance test. Similar results were documented in Troglitazone in Prevention of Diabetes (TRIPOD) and Pioglitazone in Prevention of Diabetes (PIPOD) (148,151). Many in vivo and in vitro studies with human and rodent islets have demonstrated that TZDs exert a  $\beta$ -cell-protective effect (153–157).

Pioglitazone has additional beneficial pleiotropic properties, including increased HDL cholesterol, reduced plasma triglyceride, decreased blood pressure, improved endothelial dysfunction, anti-inflammatory effects (76,158–161), and amelioration of nonalcoholic steatohepatitis (75). In addition to reduced cardiovascular events in PROactive and U.S.



**Figure 6**—Durability of glycemic control with TZDs. Summary of studies examining the effect of TZDs versus placebo or versus active comparator on HbA<sub>1c</sub> in T2DM subjects. See text for a more detailed discussion (70,82,87–92). Pio, pioglitazone; Rosi, rosiglitazone.

phase 3 trials (162,163), pioglitazone slows progression of carotid intimal-media thickness (87,152) and reduces coronary atheroma volume (88).

Physicians must be cognizant of side effects associated with TZDs including weight gain (81,164), fluid retention (162,165), bone fractures (166), and possibly bladder cancer (162,167,168) (see article on peroxisome proliferator-activated receptors in this supplement [169]). The preferred starting dose of pioglitazone is 15 mg/day titrated to 30 mg/day, which provides 70–80% of the glycemic efficacy with minimal side effects (170–174); titrating to 45 mg/day is not recommended. HbA<sub>1c</sub> lowering has been observed with a pioglitazone dose of 7.5 mg/day with minimal side effects. In a 26-week study (172) involving a Caucasian population, 7.5 mg/day pioglitazone reduced the HbA<sub>1c</sub> by 0.9% compared with placebo ( $P = 0.14$ ), while 15 mg/day reduced the HbA<sub>1c</sub> by 1.3% vs. placebo ( $P < 0.05$ ). Similar HbA<sub>1c</sub> reduction with pioglitazone, 7.5 mg/day, has been observed in an Asian population (173,174).

In combination with metformin (inhibits hepatic gluconeogenesis), pioglitazone (improves insulin sensitivity in liver/muscle and preserves  $\beta$ -cell function) offers an effective, durable, and additive therapy that retards progressive  $\beta$ -cell failure with little risk of hypoglycemia. In a 6-month trial comparing fixed-dose combination with pioglitazone (30 mg)/metformin (1,700 mg) in 600 drug-naïve T2DM patients, HbA<sub>1c</sub> declined by 1.8% (from baseline HbA<sub>1c</sub> 8.6%) and was significantly greater than the 1.0% reduction observed with metformin alone or pioglitazone alone (175). Similar results were reported by Rosenstock et al. (176) using initial combination therapy with rosiglitazone (8 mg)/metformin (2,000 mg).

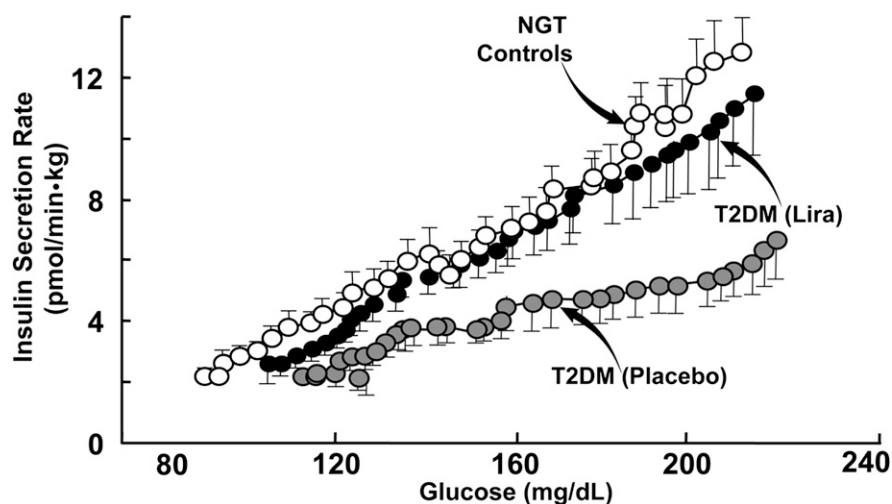
Combining pioglitazone with GLP-1 analog curbs weight gain associated with the TZD (177). Further, the natriuretic effect of GLP-1 analogs (178) mitigates against fluid retention observed with TZDs. Therefore, we advocate combined GLP-1 analog/pioglitazone therapy with or without metformin in newly diagnosed T2DM patients (3).

**Intensive therapy with insulin plus metformin: reversal of metabolic decompensation.** Newly diagnosed T2DM patients who present in poor metabolic control are markedly resistant to insulin and have severely impaired  $\beta$ -cell function. Glucotoxicity (8), lipotoxicity (8,42,62), and multiple metabolic abnormalities (3)

play an important role in the insulin resistance and  $\beta$ -cell dysfunction. Institution of intensive insulin therapy with or without other antidiabetic agents to correct these many metabolic abnormalities, therefore, represents a rational approach to therapy based upon pathophysiology. After a period of sustained metabolic control, the insulin therapy can be continued or the patient can be switched to a non-insulin therapeutic regimen. This approach has recently been examined by Harrison et al. (179). Fifty-eight newly diagnosed T2DM patients in poor metabolic control (HbA<sub>1c</sub> 10.8%) initially were treated for 3 months with metformin plus insulin to reduce the HbA<sub>1c</sub> to 5.9%. Subjects then were randomized to continued therapy with insulin-metformin combination therapy with pioglitazone/metformin/glyburide. During 3 years of follow-up, both groups maintained the reduction in HbA<sub>1c</sub>, but the insulin dose had to be increased, indicating that, despite excellent glycemic control,  $\beta$ -cell failure continued in this group. Further, glycemic control in both groups was achieved at the expense of a relatively high rate of hypoglycemia and weight gain in the insulin/metformin group, consistent with multiple studies demonstrating a high incidence of hypoglycemia in sulfonylurea-treated and insulin-treated subjects.

**Metformin plus GLP-1 analog plus pioglitazone: a pathophysiologic option that offers robust glycemic control and weight loss.** The combination of

biguanide (metformin), TZD (pioglitazone), and GLP-1 analog offers a rational treatment choice, targeting multiple pathophysiologic abnormalities in T2DM: muscle insulin resistance (pioglitazone), adipocyte insulin resistance (pioglitazone), pancreatic  $\beta$ -cell failure (GLP-1 analog, pioglitazone), hepatic insulin resistance (metformin, pioglitazone, and GLP-1 analog), and excessive glucagon secretion (GLP-1 analog) (3) with weight loss (GLP-1 analog) and low risk of hypoglycemia (93,97). Studies with exenatide have demonstrated durable glycemic control for 3 years (84,93).  $\beta$ -Cells in T2DM are blind to glucose, and GLP-1 analogs have the unique ability to restore  $\beta$ -cell glucose sensitivity (84–86) (Fig. 7) by augmenting glucose transport, activating glucokinase, increasing Pdx, and replenishing  $\beta$ -cell insulin stores (180,181). Because pharmacologic GLP-1 levels (~80–90 pmol/L) are achieved with GLP-1 analogs, they overcome  $\beta$ -cell insulin resistance and augment insulin secretion. Increased insulin and inhibited glucagon secretion reduce basal HGP, reducing fasting plasma glucose concentration and enhancing HGP suppression after a meal (98,99). Although GLP-1 analogs do not have a direct insulin-sensitizing effect, they augment insulin-mediated glucose disposal secondary to weight loss (97). The combination of pioglitazone plus exenatide reduces hepatic fat content and markers of liver damage in T2DM (182). In T2DM patients treated with rosiglitazone, exenatide, or both (as add-on



**Figure 7**—A single dose of liraglutide (Lira) (7.5  $\mu$ g/kg or 0.75 mg for 100-kg person) administered acutely completely restores  $\beta$ -cell sensitivity to glucose using the graded glucose infusion technique to evaluate  $\beta$ -cell function (86).

to metformin), improved  $\beta$ -cell function and insulin sensitivity were noted, with weight loss in all exenatide-treated groups (177). Similar results have been reported by others (182–185) with combined GLP-1 analog/TZD therapy.

In an ongoing study, we compared triple combination therapy with pioglitazone/metformin/exenatide with the standard ADA approach (metformin followed by sequential addition of sulfonylurea and then basal insulin) in 134 newly diagnosed T2DM patients with starting HbA<sub>1c</sub> 8.7% (186). After 2 years, HbA<sub>1c</sub> reduction was greater in the triple therapy versus sequential ADA group (2.7 vs. 2.2%,  $P < 0.01$ ), triple therapy subjects lost 1.5 vs. 4.1 kg weight gain with the ADA approach, and hypoglycemia incidence was 13.5-fold higher in the sequential ADA group. These preliminary results indicate that a triple combination approach focused on reversing underlying insulin resistance and  $\beta$ -cell dysfunction is superior to sequential therapy (metformin, add sulfonylurea, add basal insulin) with agents that do not correct core pathophysiologic defects in T2DM.

**DPP4i: weak but easy alternative to GLP-1 analogs.** DPP4i have gained widespread use in combination with metformin because of their weight neutrality, modest efficacy, and safety (187,188). Metformin has a modest effect to increase GLP-1 secretion (107,189). Thus, combination metformin/DPP4i therapy may result in increased GLP-1 levels (190) and an additive glucose-lowering effect (191,192). When used in triple combination with metformin plus pioglitazone (30 mg/day), alogliptin resulted in better glycemic control and fewer pioglitazone dose-dependent side effects (edema, weight gain) compared with metformin with a higher pioglitazone dose (45 mg/day) (172). Because they correct multiple components of the ominous octet, have superior glucose-lowering efficacy, promote weight loss, and preserve  $\beta$ -cell function, we favor GLP-1 analogs over DPP4i in the triple therapy approach. Nonetheless, because of their ease of administration and safety, DPP4i represent a reasonable alternative.

### Conclusions and recommendations

T2DM is a multifactorial, multiorgan disease, and antidiabetes medications should address underlying pathogenic mechanisms rather than solely reducing the blood glucose concentration. Emphasis should be placed on medications that ameliorate insulin resistance and prevent

$\beta$ -cell failure if durable HbA<sub>1c</sub> reduction is to be achieved. Further, the long-practiced glucocentric paradigm has become antiquated. Diabetic patients are at high risk for cardiovascular events, and comprehensive evaluation/treatment of all cardiovascular risk factors is essential. Simply focusing on glycemic control will not have a major impact to reduce cardiovascular risk (113,123). Therefore, we favor a therapeutic approach based not only on the drug's glucose-lowering efficacy/durability but also on its effect on weight, blood pressure, lipids, cardiovascular protection, and side effect profile, especially hypoglycemia.

Initial therapy in newly diagnosed T2DM patients without cardiovascular disease should be capable of achieving the desired glycemic goal, which should be as close to normal as possible: HbA<sub>1c</sub>  $\leq 6.0\%$ . This will require combination therapy in the majority of T2DM patients (3) (Fig. 1). While we favor the pathophysiologic approach, physicians must be cognizant of the ABCDE of diabetes management (4). An approach that emphasizes pathophysiology but allows for individualized therapy will provide optimal results. Evidence-based medicine (UPKDS) has taught us that sequential therapy with metformin followed by sulfonylurea addition with subsequent insulin addition represents the treat to fail approach, and we do not recommend this approach unless cost is the overriding concern.

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